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Efficient Synthesis and Molecular Structure of 2-Hydroxyisophthalaldehyde

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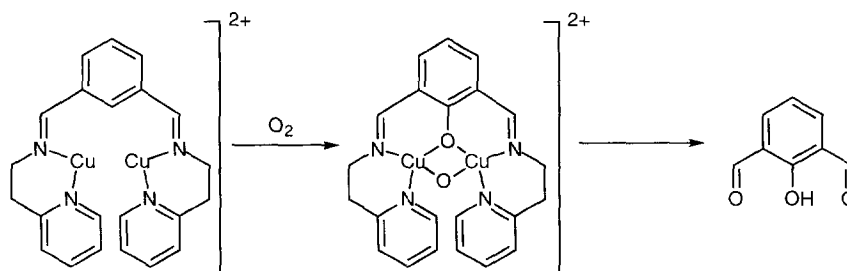
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Abstract: A new highly effective procedure has been developed for the preparation of 2-hydroxyisophthalaldehyde from 2,6-dimethylphenol. The X-ray crystal structure shows infinite chains of molecules joined by hydrogen bonds. © 1997 Published by Elsevier Science Ltd.

The activation of molecular oxygen by low molecular weight synthetic metal complexes is an area of considerable interest¹. For instance a number of dinuclear copper complexes have been prepared to mimic proteins such as haemocyanin,^{2a} tyrosinase^{2b} and dopamine- β -hydroxylase,^{2c} whose typical features are binding or activation of molecular oxygen.

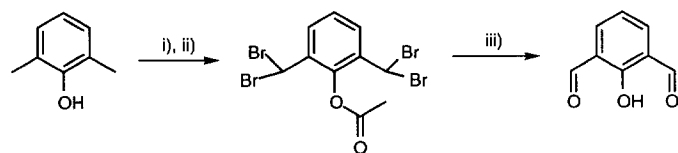
For the construction of biomimetic systems which contain multidentate nitrogen donor ligands, 2-hydroxyisophthalaldehyde has been proven to be a very useful building block.¹⁻³ The synthetic accessibility of this dialdehyde, however, is rather limited. Three general routes can be distinguished: (i) The Reimer-Tiemann reaction on phenols has been reported to yield 2-hydroxyisophthalaldehyde but only in very low yield, the major product being salicylaldehyde.⁴ (ii) A recent methodology is based on a dinuclear copper(I) complex as a tyrosinase mimic prepared by the condensation of isophthalaldehyde and two equivalents of 2-aminoethyl-2-pyridine.⁵ When this complex is reacted with molecular oxygen in solution, a rapid hydroxylation of the 2-position takes place and after removal of the copper and cleavage of the imine functionality, 2-hydroxyisophthalaldehyde is obtained (scheme 1). Drawbacks of this rather lengthy method are the sensitivity of the copper(I) complex to oxygen and water and the usage of the expensive 2-aminoethyl-2-pyridine.



Scheme 1 Synthesis of 2-hydroxyisophthalaldehyde via method (ii)

(iii) Previously we have reported a route *via* tetrabromination of 2,6-dimethylphenoxy acetate with bromine followed by acidic hydrolysis.³ This method however suffers from poor reproducibility, as it is highly dependent on the quality and dryness of the bromine and often gives variable amounts of 5-bromo-2-hydroxyisophthalaldehyde as byproduct during the hydrolysis. Here we wish to report a facile three step procedure from 2,6-dimethylphenol with good yields and good reproducibility.

In the first step 2,6-dimethylphenol is acetoxyalted using acetylchloride in dichloromethane and triethylamine (Scheme 2). After distillation 2,6-dimethyl acetoxybenzene is obtained in high yield (90%). Bromination with 4 equivalents of N-bromosuccinimide in tetrachloromethane with IR-irradiation⁶ overnight gives in 88% yield a yellow solid which is sufficiently pure for the next step. Analytically pure tetrabromide was obtained after one recrystallisation from pentane-dichloromethane.



Scheme 2. i) AcCl, NEt₃, CH₂Cl₂; ii) NBS, CCl₄, IR-irradiation, 6-10 hrs relax. iii) NaOAc, HOAc, 2 days reflux.

Finally, the tetrabromide was hydrolysed to the dialdehyde with simultaneous removal of the acetoxy group by refluxing for two days in acetic acid with excess sodium acetate,⁷ which gives the desired product as bundles of long white needles in 72% yield after recrystallisation from water. This procedure was also successfully applied to the synthesis of 5-hydroxyisophthalaldehyde from 3,5-dimethylphenol.

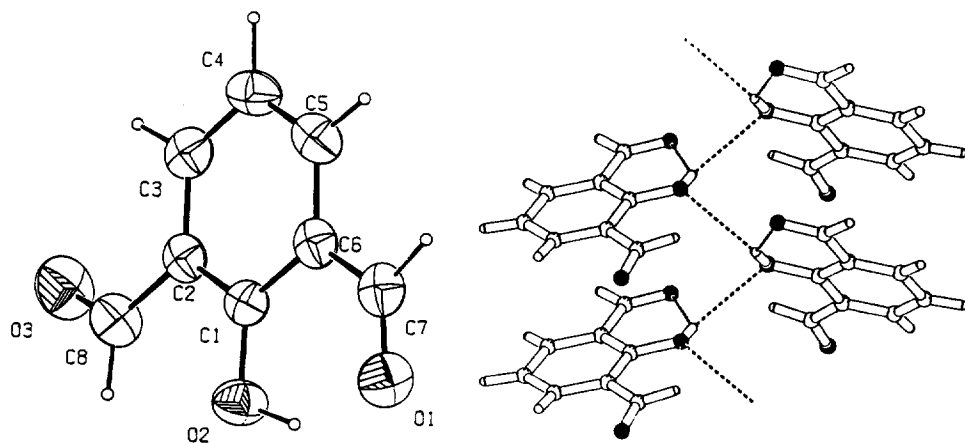


Figure 1a (ORTEP plot of 2-hydroxyisophthalaldehyde) and **1b** (crystal packing of 2-hydroxyisophthalaldehyde). Selected bond lengths [Å]: O2-H2 0.94(5), O2-C1 1.345(4), O3-C8 1.203(5), C7-H7 1.05(4), C8-H8 1.02(4); selected bond angles [°]: C1-O2-H2 110(3), O1-C7-C6 124.2(3), O3-C8-C2 124.4(3); selected dihedral angles [°]: H2-O2-C1-C2 168(4), C1-C6-C7-O1 3.2(6), C3-C2-C8-O3 4.2(6).

An X-ray crystal structure analysis of 2-hydroxyisophthaldehyde revealed some interesting features (fig. 1a). Strong intramolecular hydrogen bonding of phenolic H2 with O1 ($O1-O2=2.626(4)$ Å) is observed. An intermolecular hydrogen bond $O2-H2...O2$ [$1/2+x, 1/2-y, -z$] joins the molecules into a cooperative linear chain parallel to the z -axis as shown in figure 1b. In conclusion, we have demonstrated a simple, selective and reproducible three-step procedure for the synthesis of the valuable 2-hydroxyisophthaldehyde from 2,6-dimethylphenol with 57% overall yield. Furthermore, this procedure is readily applicable to other dimethyl substituted phenols.

EXPERIMENTAL

2,6-dimethylphenoxy acetate: This compound was prepared from 2,6-dimethyl phenol as described previously.³

2,6-($\alpha,\alpha,\alpha',\alpha'$ -tetrabromo)dimethylacetoxybenzene: 3.91 g (0.024 mol) 2,6-dimethylacetoxybenzene and 17 g (0.096 mol) N-bromosuccinimide were refluxed in 100 mL tetrachloromethane under continuous irradiation with an IR lamp until all of the white solids floated on the solution (generally 6–10 h). After hot filtration and evaporation of the volatiles, 10.1 g (0.021 mol, 88%) of the tetrabromo compound was obtained. An analytically pure sample was obtained by crystallisation from CH_2Cl_2 /pentane to give cubic white crystals. 1H NMR (300 MHz, $CDCl_3$) δ 2.51 (s, 3H); 6.63 (s, 2H); 7.44 (t, 1H, $J = 8.0$ Hz); 7.93 (d, 2H, $J = 8.0$ Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 20.8; 32.8; 127.7; 131.8; 134.3; 139.8; 167.8. Anal. found (calc.) for $C_{10}H_8O_2Br_4$: C 25.38 (25.03); H 1.72 (1.68); Br 66.02 (66.62). MS (EI): 476 (M^+), HRMS calc 475.726, found 475.726.

2-hydroxyisophthaldehyde: 10.1 g tetrabromide (21.1 mmol) and 21 g sodium acetate were suspended in 100 mL acetic acid and the suspension was heated to reflux for two days. After evaporation of the volatiles, 75 mL H_2O was added followed by extraction with three portions of 100 mL diethylether. The combined water layers were extracted with chloroform. After drying the organic layers on $MgSO_4$, the volatiles were removed and the residue crystallised from H_2O to give 2.26 g (15.1 mmol, 72%) of slightly hygroscopic long white crystals. 1H NMR (300 MHz, $CDCl_3$) δ 7.14 (t, 1H, $J = 7.6$ Hz); 7.98 (d, 2H, $J = 7.6$ Hz); 10.26 (s, 2H); 11.68 (s, 1H). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 119.8; 123.2; 137.4; 163.5; 191.8. Anal. found (calc.) for $C_8H_6O_3$: C 63.59 (64.00); H 4.15 (4.00). MS (EI): 150 (M^+), HRMS calc 150.032, found 150.032.

Crystal data for 2-hydroxyisophthaldehyde. $C_8H_6O_3$ $M_r = 150.13$, yellow, plateshaped crystal ($0.05 \times 0.15 \times 0.60$ mm), orthorhombic, space group $P2_12_12_1$ (no. 19) with $a = 3.9416(5)$, $b = 7.5591(9)$, $c = 22.616(3)$ Å, $V = 673.84(5)$ Å³, $Z = 4$, $D_x = 1.4499(3)$ g cm⁻³, $F(000) = 312$, $\mu(Cu\ K\alpha) = 9.7$ cm⁻¹. 761 Reflections measured, 741 independent, ($1.96^\circ < \theta < 68.5^\circ$, $\omega/2\theta$ scan, $T = 295$ K, Cu $K\alpha$ radiation, Ni filter, $\lambda = 1.54184$ Å) on an Enraf-Nonius CAD4-F diffractometer on sealed tube. Data were corrected for L_p effects and for a linear decay of 8% of three reference reflections but not for absorption. The structure was solved by automated direct methods (SHELXS96). Refinement on F^2 was carried out by full-matrix least-squares techniques (SHELXL-96); no observance criterion was applied during refinement. Hydrogen atoms were located on a

difference Fourier map and subsequently included in the refinement. Refinement converged at a final $wR2$ value of 0.1341, $R1 = 0.0489$ (for 617 reflections with $I > 2\sigma(I)$), $S = 1.101$, for 118 parameters. A final difference Fourier showed no residual density outside -0.23 and $0.25 \text{ e } \text{\AA}^{-3}$. Further details of the crystal structure investigation may be obtained from the Director of the Cambridge Crystallographic Data Centre, 12 Union Road, GB-Cambridge CB2 1EZ (UK) on quoting the full journal citation.

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